REMARKS

Amendments

Claims 3 and 4 are similar to canceled claims 1-2, wherein implicit determining steps are now expressly recited. Claim 5 finds support, inter alia, at p.5, line 22, and Examples; claim 6 finds support, inter alia, at p.6, line 8. These amendments introduce no new matter.

35USC103(a)

In the prior appeal in this application "the" issue of the case became a matter that is not even in contention:

> Thus, the issue in this appeal is whether there is a reasonable basis for believing that the prior PAS domain proteins meet the claimed limitation of "the PAS domain is predetermined, prefolded in its native state, and comprises a hydrophobic core that has no NMR-apparent a priori formed ligand cavity." Decision dated Sep 19, 2007

In fact, we concur that prior art teaches PAS domains without known cofactors and having tightly packed cores with no pre-formed ligand-binding cavities. We concur that prior art teaches that these PAS domains would have no NMR-apparent a priori formed ligand cavity. We concur that prior art teaches a variety of proteins that comprise PAS domains, and proposes functional assays for compounds which modulate their interactions. And we concur that prior art teaches NMR analysis of receptor-ligand (enzyme-substrate) binding.

As detailed below, one skilled in the art knows that NMR analysis of receptor-ligand has been practiced on proteins having known ligand binding sites. One skilled in the art would not have determined that a candidate target protein in fact has no NMR apparent ligand binding site, and then turned around and initiated an NMR-based screen of that very target for ligand binding.

Prior descriptions (including Fesik, WO97/18471) of "SAR by NMR" wherein structure-activity-relationships are obtained by NMR, have invariably targeted "druggable" proteins, apo-proteins structurally characterized to have preformed ligand binding pockets, proteins such as FKBP, stromelysin, E2 DNA binding domain, Erm methyltransferase, SH2 domains, etc.

In contrast, the recited PAS domains are determined to be absent any ligand binding pocket, and such proteins have not been, and would not have been screened for ligand binding by NMR because based on their structure, they were not expected to bind ligands. Further, these domains do not require protein chaperones or other cellular components to adopt a stable fold, nor do they have known ligands. Finally, PAS domains are involved in protein/protein interactions (PPIs), making them members of a class of targets that are widely considered "undruggable":

> Of the roughly 30,000 unique protein sequences that comprise the human proteome, only 1% have been successfully targeted with small-molecule drugs. Moreover, most of those fall into the same few structural or functional families, the two most common being enzymes and G-protein-coupled receptors (GPCRs). These successfully targeted proteins typically share the property that the natural substrates or ligands with which they interact are themselves small organic molecules such as metabolites and neurotransmitters. Historically there has been notably little success in developing drug-like inhibitors of proteins whose natural ligands are other proteins. Screening of such targets against pharmaceutical company compound libraries has rarely produced useful hits or leads (Fig. 1). Consequently, these protein-protein interaction (PPI) targets have come to be considered as intractable with respect to small-molecule drug discovery, or 'undruggable' in industry jargon.
> Whitty et al. Nature Chemical Biology 2, 112-118 (2006), p.112, first para. (attached).

Our claims are specifically directed to a method of detecting binding of a PAS domain of a protein with a foreign core ligand of the PAS domain, wherein the PAS domain is prefolded in its native state. The method specifically requires the steps of: (a) determining from NMR analysis of the PAS domain that the PAS domain comprises a hydrophobic core that has no NMR-apparent a priori formed ligand cavity; (b) detecting a first NMR spectrum of the PAS domain in the presence of a foreign ligand; (c) comparing the first NMR spectrum with a second NMR spectrum of the PAS domain in the absence of the ligand; and (d) determining the presence of the ligand specifically bound within the hydrophobic core of the PAS domain.

As explained in our Specification some members of the PAS family are known to contain small molecule cofactors within their cores, and these cofactors are reportedly required for proper folding and functioning of the PAS domain within the context of the holo-protein. Specification,

p.1, line 22 - p.2, line 1. However, for most PAS domains there is no evidence for such a cofactor. In fact, structurally characterized PAS domains without bound cofactors (Amezcua et al., 2002; Erbel et al., 2003; Morais Cabral et al., 1998) show tightly packed cores with no pre-formed cavities that would suggest a cofactor or ligand binding site. Specification, p.2, lines 2-5.

Since the prior work provided no evidence of cofactors for most PAS domains, and taught that those limited PAS domains having cofactors required them for proper folding, and taught that PAS domains without cofactors had tightly packed cores with no pre-formed cavities that would suggest a cofactor or ligand binding site, one skilled in the art would not have suspected that such PAS domains (without known cofactors and having tightly packed cores with no pre-formed cavities that would suggest a cofactor or ligand binding site) would be rational candidates to screen for core ligand binding; in fact, the prior art teaches squarely away from such use.

Though the cited art does not support a prima facie case for obviousness, for good measure we provide affirmative evidence documenting the fact that one skilled in the art would have considered the claimed invention nonobvious at the time it was made (attached expert Declaration).

Please charge our Deposit Account No.19-0750 (order UTSD:1510) all necessary fees for this communication.

Respectfully submitted,
SCIENCE & TECHNOLOGY LAW GROUP

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Enc. Whitty et al. Nature Chemical Biology 2, 112-118 (2006)
Declaration under 37CFR1.132

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